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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,247	08/14/2006	Tatsuya Nakai	294136US0X PCT	6936

22850 7590 05/28/2010

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EXAMINER	
CHUI, MEI PING	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
05/28/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/589,247	NAKAI ET AL.	
	Examiner	Art Unit	
	MEI-PING CHUI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-14,17-22 and 24-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7-14, 17-22, 24-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on 12/17/2009 is acknowledged. Claims 1, 4, 7-14, 17-22, 24-27 are pending in the application.

Status of Claims

Accordingly, claims 1, 4, 7-14, 17-22, 24-27 are presented for examination on the merits for patentability.

Rejection(s) not reiterated from the previous Office Action are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4, 7-14, 17-22, 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sawayanagi et al. (U. S. Patent No. 5,296,235) and Hidaka et al. (U. S. Patent No. 5,225,199) combined, and in view of Dasseux, J. L. H. (U. S. Patent Application Publication No. 2005/0101565).

Applicants Claim

Applicants claim an external preparation, i.e. plaster or poultice, comprising: (**A**) atorvastatin, or pitavastatin, or a salt thereof, (0.001-20 % by mass of the external preparation) and (**B**) at least one monoterpene (0.01-15 % by mass relative to the total amount of the external preparation); wherein (i) the monoterpene can be menthol, terpineol or citronellal, or a combination thereof; (ii) the external preparation further comprises: liquid paraffin, the styrene-isoprene-styrene copolymer and those recited therein; (iii) the preparation does not contain ethanol.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Sawayanagi et al. teach a plaster preparation that is suitable for cutaneous application and can avoid the risks of side effects caused by the drug, such that the use of the drug in the form of a plaster can help to promote the clinical utility of the drug (column 1, background section).

Sawayanagi et al. teach that the plaster preparation, which contains the active drug, can comprise a combination of constituents, such as:

(i) water-soluble polymers, polyacrylic acid and/or sodium polyacrylate, preferably in 0.5-10 % by weight of the plaster preparation (column 2, lines 14-25);

(ii) an absorbefacient compound for promoting cutaneous absorption, i.e. propylene glycol, menthol and the like, in 0.1-15 % by weight of the plaster preparation (column 2, lines 26-33);

(iii) additives that are commonly added to conventional hydrophilic base-type plaster preparation: polyhydric alcohols, i.e. sorbitol, glycerol; inorganic fillers, i.e. kaolin (4 grams); surfactants, i.e. polyethylene glycol monolaurate; pH modifiers and the like (column 2, lines 34-45; column 3-4, Example 1);

(iv) hydrophobic polymers, i.e. styrene-isoprene-styrene block copolymer in 0.2-20 %, or 30-99.5 % by weight of the plaster preparation (column 2, lines 58-61, line 65 to column 3, line 3);

(v) additional additives that are commonly added to conventional hydrophobic base-type plaster preparation, i.e. aliphatic hydrocarbon resins; plasticizer, i.e. liquid paraffin; pH modifiers (column 3, lines 1-14);

(vi) other additional additives, i.e. 70 % aqueous solution of D-sorbitol (15 grams); water; glycerin (15 grams) (column 3-4, Example 1).

Sawayanagi et al. also teach that, for a plaster preparation, the composition typically comprises 0.5-20 % by weight of the drug (column 3, lines 31-34).

With respect to the component "tartaric acid", it is known that tartaric acid is a common pH adjusting agent.

With respect to the claim limitation where the external preparation does not contain ethanol, the teaching of Sawayanagi et al. meets the limitation because it does **not teach the use of ethanol in the preparation of plaster is necessary and none of the examples contain ethanol.

Hidaka et al. teach a preparation of a transdermal plaster, which is capable of enhancing the absorption for clinically effective drugs for human skin application, comprising inorganic fine particles, i.e. silicate salts or aluminosilicate compounds; a usual adhesive, i.e. polyisoprene rubber; a diffusion auxiliary, i.e. polyethylene glycol, sorbitol, fluid paraffin, water (column 3, lines 45-49; column 4, lines 17-19; column 6, lines 12-14; column 7, lines 15-18; column 14, lines 56-66).

Hidaka et al. also teach that the inorganic fine particles, i.e. silicate salts or aluminosilicate compounds, is desirably presented in an amount between 0.001-1 % by weight in order to avoid skin rash (column 6, lines 29-34).

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

(1) Sawayanagi et al. and Hidaka et al. do not teach the drug uses in the plaster is pitavastatin, or atorvastatin, or a salt thereof, as claimed.

(2) Sawayanagi et al. and Hidaka et al. do not teach the preparation is a poultice or the preparation contains carmellose sodium and the amounts, as claimed.

(3) Sawayanagi et al. and Hidaka et al. also do not teach the monoterpene used in the plaster preparation is terpineol or citronellal, or a combination thereof, as claimed. However, the deficiencies are cured by Dasseux, J. L. H.

Dasseux, J. L. H. teaches statins, i.e. pitavastatin, atrovastatin, and the pharmaceutically acceptable salt thereof, are inhibitors of cholesterol synthesis block cholesterol synthesis by inhibiting HMGCoA, the key enzyme involved in the cholesterol biosynthetic pathway. However, side effects, including liver and kidney dysfunction which associated with the use of these drugs have been reported (page 4: [0024]; page 11: [0086]). Dasseux, J. L. H. thus teaches that a pharmaceutical composition that comprises pharmaceutical active agent, i.e. statins, for treating, preventing, or managing cholesterol, dyslipidemia disorders and methods of reducing or avoiding an adverse effect associated with such active agent therapy would be desirable (page 6: [0044], [0049]).

Dasseux, J. L. H. also teaches the composition can be used in the preparation of different suitable dosage forms, i.e. transdermal in the forms of a plaster or cataplasm (e.g. poultice), for administration to a patient (page 17: [0206]). Dasseux, J. L. H. further teaches that a suitable amount of disintegrant (preferably in 1-5 % by weight), i.e. croscarmellose sodium, can be used in preparing the dosage form, depending on the type of formulation (page 18: [0224]).

Finding of prima facie obviousness Rational and Motivation

(MPEP 2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Sawayanagi et al. and Hidaka et al. with Dasseux, J. L. H. to arrive at the instant invention.

One of ordinary skill would have been motivated to employ statins, i.e. pitavastatin or atrovastatin, in the preparation of a plaster for transdermal delivering these drugs to a patient because oral administration of these drugs would cause unwanted side effects, such as liver and kidney dysfunction; therefore an alternative delivery route that can help to avoid the risks of side effects caused by the drug and can promote the clinical utility of these drugs would be favorable and desired, as suggested by the prior art.

One of ordinary skill in the art also would have been motivated to incorporate common additives, i. e. polyethylene glycol or disintegrant, into a plaster preparation and then modify the amounts of these additives to a desirable level, depending on the type of selected formulation, as taught by Hidaka et al. and Dasseux, J. L. H.

With respect to the recitation of monoterpene is terpineol or citronellal as claimed, the prior art Sawayanagi et al. teach the plaster preparation uses menthol as an absorbefacient compound for promoting cutaneous absorption; such teaching would motivate one of ordinary skill in the art to try not only menthol, but also to try other monoterpenes, i.e. terpineol and citronellal, because menthol, terpineol and citronellal are all functional equivalent monoterpenes; and thus, they can be used interchangeably.

From the teaching of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed external formulation. Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed on 12/17/2009 have been considered but they are not persuasive.

Applicants argue that the instantly claimed pitavastatin and pranoprofen taught by Sawayanagi et al. are two compounds having different biological functions, different mechanisms of action and very different in structure, and therefore have different physical properties as well. Thus, while 1-menthol, employed by Sawayanagi as an absorbefacient, may promote cutaneous absorption of pranoprofen, there is no reasonable expectation to think that it would promote cutaneous absorption of a different chemotype (e.g., a statin) that has different biological properties, a different mechanism of action, a different chemical structure, and different physical properties from pranoprofen (see Remarks: page 8).

The arguments are not persuasive. Although 1-menthol is used as an absorbefacient to promote cutaneous absorption of pranoprofen in the prior art Sawayanagi et al., 1-menthol is a well known dermal penetration enhancing agent in the relevant art employed for pharmaceutical active drugs, as evident by Tsuk, A. G. (U. S. Patent No. 4,933,184), which utilizes menthol to enhance the percutaneous transfer of systemically active drugs in mammals (column 2, lines 35-53). Tsuk, A. G. also teaches a variety of active drugs that can be employed with menthol, i.e. antidiabetics drug (e.g. chlorpropamide); estrogens; beta blocker (e.g. propanolol); or lipid, cholesterol and triglyceride affecting agents (e.g. acrifran) (see column 3, lines 34-68; and all Examples).

Further evident by Lu et al. (U. S. Patent No. 5,446,025), which teaches the utilization of a mixture of menthol, camphor, methyl salicylate and urea as cutaneous membrane penetration enhancing component for effective transport leuprolide free base across human skin (column 3, lines 4-17).

Other evident by Davis et al. (U. S. Patent No. 5,665,378), which teaches a transdermal therapeutic formulation comprising capsaicin, a nonsteroidal inflammatant and pamabrom to alleviate pain or discomfort in a mammal by being applied to the skin of the mammal in the form of a patch (see Abstract and column 4, lines 23-32). Davis et al. also teaches that formulation contains skin permeation enhancers, i.e. menthol, in an amount sufficient to enhance skin permeation of one or more of the substances contained in the formulation (see column 3, lines 27-34).

Other evident by Song et al. (U. S. Patent Application Publication No. 2004/0033254), which teaches that a transdermal drug delivery contains an enhancer layer sandwiched comprising terpene as one of the absorption enhancers, which would increase the absorption of the active drug and wherein the terpene can be menthol (page 5: [0051-0052]).

Since 1-menthol is well known in the relevant art used as a skin penetration enhancer and has been successfully assisted the absorption of those pharmaceutical active drugs into the skin, such well-known knowledge, as taught by the evidences and the prior art set forth above, it would provide the motivation for one of ordinary in the art to select menthol for assisting the permeation and absorption of a statin drug into the skin.

From the teaching of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed external formulation.

Therefore, the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be

reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/H. C./

Examiner, Art Unit 1616

/Mina Haghighatian/
Primary Examiner, Art Unit 1616